REMARKS

This Amendment responds to the November 27, 2007 Office Action in which the Examiner rejected claims 1-5 and 10-14. In response, applicant has amended claims 4-5 and those dependent thereon, and has cancelled claims 6-9. Reconsideration and reexamination are respectfully requested in view of the foregoing amendments and the following remarks.

The §112 Rejections

Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asks applicants to clarify what is meant by "which fraction may be a different one in the different complexes."

In response, applicants have amended claims 4-5 to clarify the phrase on which the Examiner has focused, and to clarify it by inserting clearer reference to the antecedent basis of "fraction" and the phrase in which it appears.

Applicant submit that the foregoing amendments to claims 4-5 and the accompanying remarks overcome the §112, second paragraph, rejection of these claims as indefinite. Withdrawal of the rejection is respectfully requested.

The Anticipation Rejection

The Examiner rejects claims 1-5 and 10-13 under 35 U.S.C. §102(b) as being anticipated by Cox, for the reasons stated in a previous Office Action.

The Examiner asserts that the Cox '697 teaches a saponin vaccine preparation comprising Quillaja saponaria from 50% to 70% by weight of Fraction A of Quil A and from 50% to 30% by weight of Fraction C of Quil A, and a method of making an immunostimulatory complex (15 com), having that composition. The Examiner states that peptides can be incorporated into iscoms either directly or by chemical coupling to a carrier protein. The Examiner states that the entire complex confers immonostumulatory effects; that Table 1 shows Fractions A, B, and C of Quil A displaying different iscom forming ability and adjuvant activity; that Cox '697 shows particular combinations of Fraction A and C result in a saponin preparation that has the desirable properties of A and the benefits of C, which the Examiner contends shows that different types of saponin fractions are used to form different iscoms. Further, the Examiner states that Table 5 shows virus and iscoms, virus and iscom-matrix, and virus alone as adjuvants to confer immunogenicity. This leads the Examiner to conclude that the reference teaches that there is different type of iscoms with different types of formulations and different proteins to form the desired matrices.

Applicants respectfully request reconsideration, and maintain that the subject claims are not anticipated by the Cox '697. Cox discusses a purification procedure of fractions A, B and C of Quil A (hereinafter QHA, QHB and QHC), for which the nomenclatures in the present invention are Fractions A, B and C. The Cox patent also discusses the incorporation of each one of these fractions solitary into matrix for comparison purposes. However, the Cox patent relates to

the combination of 50% to 70% of QHA and 50% to 30 % of QHC into the same matrix particle, i.e. in the same entity. This patent does not mention or suggest a mixture of iscom or iscom matrix particles involving separating the fractions of Quil A into separate particles.

The Cox patent also teaches that QHA and QHC in the same 703 matrix particle enhances immunogenicity and that the side effects are acceptable. Despite this information in the Cox patent, the 703 formulation is no longer used therapeutically, due to its toxicity.

Most importantly, nowhere does the Cox patent mention that the different saponins should be formulated in physically different particles. On the contrary, the examples all focus on the alleged advantage of mixing the two saponin components.

The Examiner asserts that Cox teaches that different types of saponin fractions are used to form different iscom particles. While this may be true, these iscom particles comprising QHA and QHC of Quil A respectively are never immunized and tested together as in the present invention. This is also not suggested in the patent.

Thus, the preparation from which the iscom matrix is prepared comprises both QHA and QHC of Quil A. Consequently, the Cox method of cannot possibly result in a composition comprising an iscom matrix containing only QHA of Quil A and another iscom matrix comprising only QHC of Quil A. As such, Cox does not

disclose the identical invention as claimed herein and therefore cannot be found anticipating.

The present invention decreases the toxicity (the side effects) of mixtures of Quillaja saponin fractions (sub fragments of Quil A by making different iscom/iscom-matrix particles containing only one fraction (a sub fragment of Quil A), each and then mixing the individual iscom/iscom-matrix particles. Such a formulation is fundamentally different than the ones described in Cox.

The present application teaches that when two saponin fractions i.e. Fraction-A and Fraction-C are formulated in physically separate particles, the toxicity of this formulation is substantially reduced and can be administered to the vaccine with high degree of comfort. This was indeed unexpected. Concretely, Balb/c mice tolerate doses in the formulations according to the present invention (group 1 in Table 2 of the present application) that are lethal if these fractions are combined in the same particles (group 8 in Table 2).

No data demonstrating the lower toxicity of the 703 ISCOM versus QHB and QHC ISCOMs are presented in the Cox patent. To applicants' knowledge, such data has never been obtained. On the contrary, the QH703 ISCOMs were surprisingly toxic, in the same order or ever more toxic than QHC(Fraction) ISCOMs. Considering that the QHA (Fraction A) component is virtually non-toxic and that the amount of QHC is only 30% in the QH703 preparation one would expect a 67% reduction of toxicity instead or as noted a retained or even increased toxicity.

To date doses up to 100µg of saponins in the composition of the present invention have been repeatedly used without discomfort and not a single death in mice.

Based upon this different composition, the Examiner's assertion that Cox anticipates the claimed invention is simply incorrect.

The §103(a) Obviousness Rejection

The Cox patent shows that individual saponin Fractions A, B and C can be used to form ISCOM particles. The immunogenicity of these different ISCOM particles comprising a low (0.1 µg) or a higher (6 µg) dose of HA (hemagglutinin from Flu virus) combined with a high (15 µg) or a low (6 µg) dose of saponin is shown in Table 4. The different individual ISCOM particles each made from a single fraction of saponin was compared to ISCOM particles made from a mixture of Fraction A and Fraction C material composed of 70% (w/w) Fraction A and 30% Fraction C in the same particle. This particular saponin mixture is denoted QH703 and the ISCOM particles produced from the 703 mixture are called 703-ISCOM. The overall best performance (protection against challenge infection and antibody response) was noted with the Fraction B and the QH703 saponins. The least efficient saponin was Fraction A inducing poor antibody responses also at high doses of Fraction A (15 µg) and HA (1 µg).

Applicants concluded that "the experiments show that the use of QH703 permits at least the same immunogenicity and efficacy as shown by the more toxic Fractions of Quil A but with a much lower level of those toxic components"

(i.e., Fraction B and Fraction C). However, no data demonstrating the anticipated lower toxicity of the 703 ISCOM versus Fraction B and Fraction C ISCOMs are presented.

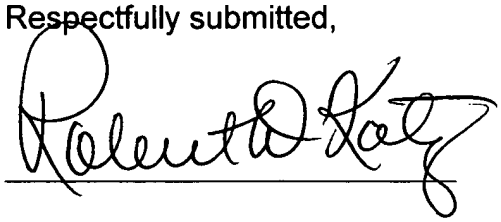
The present invention focuses on the formulation of ISCOM preparations that can be used with great comfort and minimal side effects, not to mention toxicity, in doses that are highly efficacious resulting in formulations with a wide margin between efficacy and side effects. The adjuvant formulations can be formulated for prophylactic and therapeutic uses (vaccines) with very good safety profiles even for sensitive individuals. Thus, the present invention overcomes the problems with previous ISCOM adjuvant as disclosed in Cox.

Furthermore, there is a synergistic effect in the adjuvanted antibody response. First, the magnitude of the IgG1 responses is increased. Second, there are pronounced features of both TH1 (IFN gamma and IgG2a antibody subclass) and TH2 (IL-5 and IgG1 antibody sub class) type of immune responses. This could not be forseen from the cited Cox patent. For these reasons, applicants submit that the present obviousness rejection should be reconsidered and withdrawn.

The Director is authorized to charge any fee required in connection with this response to Deposit Account No. 03-3125. If any extension is required in connection with the filing of this response, applicants hereby request same and authorize the fee therefor to be charged to Deposit Account No. 03-3125.

Dated: May 27, 2008

Respectfully submitted,



Robert D. Katz, Esq.
Registration No. 30,141
Cooper & Dunham LLP
Customer No. 23432
1185 Avenue of the Americas
New York, New York 10036
patentdocketing@cooperdunham.com
Tel. No. (212) 278-0400
Fax No. (212) 391-0525

Attorney for Applicants